

The Management of Pemphigus Vulgaris in a Burn Intensive Care Unit: A Case Report and Treatment Review

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Pemphigus vulgaris is a rare, potentially fatal, autoimmune blistering disease of the skin and mucous membranes. Treatment of this disease is problematic because of a lack of high-grade, evidence-based recommendations, the side-effect profiles of the therapies available, and the extensive supportive care that afflicted patients require. The authors present the unfortunate course of a patient with severe pemphigus vulgaris who was admitted to the U.S. Army Institute of Surgical Research Burn Center, to demonstrate the potential complications of therapy. Given the patient's complex course, the authors reviewed the literature and share in this article the most up-to-date treatment recommendations for patients with pemphigus vulgaris. The authors' review of the literature supports using conventional therapy consisting of high-dose corticosteroids and an adjuvant immunosuppressant for mild to moderate cases of pemphigus vulgaris. The immunosuppressants recommended are mycophenolate mofetil, azathioprine, and cyclophosphamide, in order of preference, based on their side-effect profiles and steroid-sparing effects. For severe or recalcitrant cases of pemphigus vulgaris, the authors recommend adding rituximab as early as possible. If increased risk of infection is of particular concern, the use of intravenous immunoglobulin in place of rituximab is advised. (J Burn Care Res 2014;35:e357–e363)

The diagnosis of pemphigus encompasses a group of potentially fatal, autoimmune blistering diseases of the skin and mucous membranes. Pemphigus is rare, with an incidence of 0.75 to 5 cases per million people each year.¹ It affects patients of all races but is more common among Greeks, Indians, and Ashkenazi Jews.² There is no sex predilection, and the approximate age of onset is 50 to 60 years.³ Pemphigus is caused by immunoglobulin G autoantibodies

directed against desmoglein 3 and/or desmoglein 1, which are structural proteins that help maintain cellular adhesion in the epidermis.⁴ The mechanism of autoantibody formation is complex, but results from a breakdown in immunologic tolerance.⁵ Pemphigus is thought to result from a two-hit mechanism with a genetic predisposition followed by exposure to a trigger, such as a medication.⁵ Medications that have been implicated include thiols, angiotensin-converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, aspirin, rifampicin, levodopa, phenobarbital, interferon, interleukin, propranolol, and nifedipine.⁵

As a result of the disruption in keratinocyte adhesion, afflicted patients develop epidermal acantholysis resulting in painful, flaccid bullae involving the mucosa and skin that quickly rupture, leading to erosions and ulcerations.⁶ If treated appropriately, the lesions typically do not scar but may leave behind postinflammatory hyperpigmentation.⁷ Pemphigus is characterized by a positive Nikolsky's sign, meaning that lateral pressure applied to normal-appearing

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The opinions or assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

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skin located adjacent to a lesion will produce separation of the overlying epidermis.⁷

The diagnosis of pemphigus is based on histology, immunological tests, and the clinical presentation. In a patient with findings suspicious for pemphigus, a skin or mucosal biopsy is needed to evaluate the histology and perform direct immunofluorescence.⁸ In pemphigus vulgaris (PV), histology will demonstrate intraepidermal acantholysis, and direct immunofluorescence testing will reveal intercellular immunoglobulin G throughout the epidermis. Indirect immunofluorescence may be used to differentiate PV from the other subtypes, such as pemphigus foliaceus and paraneoplastic pemphigus.⁹

The goal of pemphigus treatment is to reduce the autoantibody burden to prevent further acantholysis and to allow for lesion healing.¹⁰ Corticosteroids are the mainstay of current therapy, often with immunosuppressants to reduce the likelihood of side effects associated with long-term use of corticosteroids.⁸ However, there are cases of severe PV that are refractory to conventional therapy and require treatments that more directly and quickly target the pathogenic autoantibodies.¹¹ The newer augmentative therapies aim to reduce levels of disease-mediating autoantibodies in several ways. Rituximab is a monoclonal antibody that targets naïve B-cells that would mature to produce more of the autoantibodies. Intravenous immunoglobulin (IVIG) lowers serum levels of these autoantibodies but the mechanism is unclear. Last, plasmapheresis has been used as a salvage therapy to physically remove autoantibodies.¹¹ The following case report describes the clinical course of a patient treated for severe PV at the U.S. Army Institute of Surgical Research (USAISR) Burn Unit, including his treatments and the complications arising from the treatments.

CASE REPORT

A 47-year-old, Hispanic man was transferred to the U.S. Army Institute of Surgical Research Burn Center for management of severe PV involving 60 to 70% of his total body surface area. Symptoms had begun 6 to 8 weeks before his arrival. He had been managed in a civilian hospital for the previous 7 days on prednisone (60 mg/day). His physical examination was notable for crusted erosions on his lips; diffuse mucosal erosions of the entire oropharynx; and extensive erosions and crusting on his scalp, face, trunk, buttocks, and upper and lower extremities. Diagnosis was verified with direct and indirect immunofluorescence testing in addition to routine histology.

The patient's course at the Burn Center was highlighted by a series of medical interventions, which resulted in brief periods of clinical improvement. Unfortunately, his course was repeatedly complicated by adverse events necessitating acute management, which delayed treatment of his underlying PV. The series of interventions and adverse events is summarized in Table 1.

DISCUSSION

For the last 60 years, the cornerstone of PV therapy has been corticosteroids. More recently, immunosuppressants have been used as adjuvant therapy to decrease the incidence of corticosteroid-associated side effects. However, immunosuppressants also have side-effect profiles and may lead to adverse effects as well.^{8,11} Newer augmentative therapies that reduce the cumulative amount of corticosteroids and immunosuppressants are increasingly being used. These treatments are especially valuable in cases of severe, refractory PV. In these cases, symptoms are often inadequately controlled with conventional therapy and the risks of adverse effects continue to accumulate. More aggressive treatments like rituximab and IVIG are increasingly being used in these cases of refractory PV in order to more directly and expeditiously reduce the autoantibody burden.¹¹

The evidence-based treatment of PV is challenging as its rarity has precluded the completion of many large-scale, randomized controlled trials. Historically, pemphigus has been a lethal disease with mortality rates as high as 90%, with 75% of patients dying within 1 year.^{2,3} With the advent of systemic corticosteroids in the 1950s, mortality rates were drastically reduced to an average of 30%.⁸ Unfortunately, the high doses of corticosteroids required to treat severe PV (1–2 mg/kg/day) can cause a number of serious side effects, including diabetes, osteoporosis, adrenal suppression, Cushing's syndrome, cataracts, intestinal perforation, and increased susceptibility to infection.⁸ Currently, most deaths associated with pemphigus are the result of corticosteroid-related complications and not from the disease process itself.¹³

Immunosuppressants are commonly used with high-dose corticosteroids to reduce the total dose of corticosteroids required for disease control, thus reducing the number of side effects.¹⁴ Several immunosuppressants have been used, but the most commonly used and studied are azathioprine (2 mg/kg/day), mycophenolate mofetil (2–3 g/day), and cyclophosphamide (2 mg/kg/day).^{9,14–22} With the addition of these therapies, mortality associated with PV has been reported to be low as <10%.¹³

Table 1. Summary of interventions and adverse events

Hospital Day	Intervention or Adverse Event
0	Oral prednisone initiated, 60 mg/day Fluocinonide 0.05% ointment to open wounds three times a day Gentle skin debridement and wound care with Silverlon® dressings (Silverlon, Chicago, IL)
3	Bacteremia Corticosteroids rapidly tapered to prevent exacerbating underlying infection
12	Surveillance cultures negative Oral prednisone 60 mg/day resumed with dosage goal of 1 mg/kg/day
14	Acute kidney injury attributed to either vancomycin or tobramycin Delirium attributed to corticosteroids Oral prednisone tapered 3-day course of intravenous immunoglobulin started
18	Cecal perforation partially attributed to corticosteroids ¹² Exploratory laparotomy with right hemicolectomy and end ileostomy with delayed primary closure
20	Altered mental status leading to airway/respiratory compromise Patient intubated and placed on mechanical ventilation Minocycline given for presumed sepsis IV administration of solumedrol 80 mg/day and mycophenolate mofetil 1 g/day initiated Blood and bronchoalveolar lavage fluid demonstrated multidrug resistant <i>Pseudomonas aeruginosa</i> Antibiotics de-escalated to administration of colistimethate 325 mg twice a day and nebulized colistimethate 150 mg every 6 hours Corticosteroids continued
31	Mycophenolate mofetil increased to 2 g/day IV administration of solumedrol continued at current dose of 80 mg/day
34	Patient transitioned from solumedrol to prednisone 80 mg/day Mycophenolate mofetil discontinued Azathioprine 50 mg/day started Fascial dehiscence of abdominal wound site from previous exploratory laparotomy and hemicolectomy, which was attributed to corticosteroids Dehiscence repaired without incident
36	Rituximab 1000-mg infusion given Oral prednisone decreased to 60 mg/day the following day Patient continued to show clinical improvement and was extubated
41	Azathioprine increased to 100 mg/day Prednisone decreased to 45 mg/day in anticipation of a prolonged taper
63	Leukopenia (1.9×10^3 cells/mm ³) attributed to azathioprine Azathioprine subsequently discontinued To supplement systemic treatments: topical clobetasol 0.5% ointment to affected areas and dexamethasone 0.5 mg/5 ml oral swish and spit 4 times a day were initiated
67	Worsening oral involvement noted Rituximab 375 mg/m ² (700-mg dose) once with plan to continue dosing once a week for 4 weeks in addition to prednisone 45 mg/day
103	Sepsis presumably caused by “possible fungal growth” visualized in 3 × 3 cm sacral wound with purulent drainage Patient reintubated and given vasopressors because of increased work of breathing, hypotension, and fever Family requested that his code status be changed to “do not resuscitate”
114	Bacteremia with <i>Acinetobacter baumannii</i> Vancomycin and meropenem initiated
119	Patient could not be adequately oxygenated Focus of care transitioned to comfort measures only Patient died shortly thereafter

The most current guidelines on the use of immunosuppressants comes from a year-long randomized controlled trial of 120 patients who received four different treatment regimens for PV, including

prednisolone alone; and combination therapies of prednisolone with azathioprine; with mycophenolate mofetil; and with IV-pulsed cyclophosphamide.¹⁴ The immunosuppressants were similarly efficacious



Figure 1. The patient: a 47-year-old Hispanic man with severe pemphigus vulgaris. Shown here are diffuse skin erosions and crust on his dorsal trunk, buttocks, and proximal upper and lower extremities.

and achieved significant steroid-sparing effects, with azathioprine having the greatest benefit (34% reduction); followed by pulsed cyclophosphamide (29% reduction); and finally mycophenolate mofetil (16% reduction).¹⁴ In addition, another randomized controlled trial evaluating prednisone with either placebo or mycophenolate mofetil for the induction of remission was conducted. This study noted that patients receiving mycophenolate mofetil had a shorter time to induction and a longer duration of response.²³ Two randomized controlled trials comparing cyclosporine and corticosteroids with corticosteroids alone failed to show a treatment advantage of cyclosporine in PV, and one study showed an increased incidence of adverse events in the cyclosporine arm.^{24,25} No randomized controlled trials using methotrexate in PV patients have been conducted.¹¹

While helpful as steroid-sparing agents, immunosuppressants have side-effect profiles of their own. Common side effects of azathioprine include myelosuppression, nausea, hepatotoxicity, and increased susceptibility to infection.¹¹ Cyclophosphamide has a side-effect profile including hematuria; increased susceptibility to infections; and increased risk of transitional cell bladder cancer, which limits its use as an adjuvant therapy.²² Mycophenolate mofetil is considered well-tolerated and relatively less toxic in comparison with other immunosuppressive agents; however, patients may still develop gastrointestinal intolerance and neutropenia.¹¹

Over the past several years, rituximab has been increasingly used in the treatment of refractory PV.^{26–31} Randomized controlled trials are currently in progress, but multiple case series have provided evidence of its benefit in the treatment of pemphigus. A 2012

review, which included 42 studies and 272 patients, analyzed treatment results based on the dosage protocol used in the studies: those studies that used the lymphoma protocol (4 weekly doses of 375 mg/m²) or those that used the rheumatoid arthritis protocol (1000 mg, 15 days apart). At a mean 18-month follow-up, complete remission was achieved in 66.66% of those patients on the lymphoma protocol and in 75% of those on the rheumatoid arthritis protocol.³² An additional 12.78% and 23.91% demonstrated partial remission on the lymphoma and the rheumatoid arthritis protocol, respectively.³²

More study is needed to determine the optimum dosing of rituximab, with the 2012 review finding no distinct advantage to using either the lymphoma or the rheumatoid arthritis protocol. The review also noted that the incidence of serious infection was 3.9% in the lymphoma protocol and 15.21% in the rheumatoid arthritis protocol with a respective mortality rate of 2.22% and 1.09%. These findings suggest a risk of immunosuppression with rituximab, but this risk is difficult to assess because all but 2 of 272 patients studied were also on other immunomodulating therapy for their PV. Additional drawbacks to rituximab therapy are its high cost and lack of known long-term side effects.³²

IVIG is a relatively new treatment modality for pemphigus. It can rapidly control disease activity and is believed to work by selectively lowering serum levels of disease-mediating autoantibodies.^{33–36} It is usually administered at a dose of 2 g/kg of body weight, delivered over 3 to 5 days and repeated every 2 to 6 weeks.^{33–36} In a recent retrospective study, the coadministration of IVIG and an immunosuppressant was able to rapidly lower serum autoantibodies

in 20 patients with PV and this effect was significantly enhanced than with IVIG alone.³⁷ As monotherapy, a recent randomized controlled trial evaluated response in patients with steroid-resistant pemphigus to IVIG dosages of 200 mg/day or 400 mg/day in comparison with a placebo.³⁸ The study found that patients receiving 400 mg/day had much lower disease activity and could be maintained on this treatment much longer without the need for additional therapy.³⁸ Another randomized, placebo-controlled, crossover trial of IVIG that was conducted in a single patient with refractory pemphigus showed lower disease activity and serum autoantibody levels during treatment with IVIG. The patient underwent two phases of treatment consisting of 6 consecutive months of either IVIG or placebo infusion in conjunction with prednisolone and azathioprine.³⁹

IVIG has an excellent safety profile in comparison with other treatment modalities for pemphigus, with mild side effects that include headache, fever, chills, myalgia, flushing, hypotension, tachycardia, and gastrointestinal symptoms.¹¹ Additionally, it should be noted that a recent case series of eight pregnant patients with PV who were treated with IVIG showed a good response, without any apparent signs of complications from treatment in the mother or the fetus. IVIG may be considered as another possible therapeutic option in pregnant patients with pemphigus.⁴⁰

Increasingly, rituximab is being used in conjunction with IVIG. In one prospective case series, 11 patients with extensive PV who failed standard therapy were given rituximab (375 mg/m²) weekly for three successive treatments and then IVIG (2 g/kg) for the fourth week. This induction cycle was repeated the following month, and then a single dose of each medication was administered monthly for the next 4 months.²⁸ Nine of the 11 patients experienced rapid remission lasting an average of 31 months without any infections or rituximab-related side effects.²⁸ A more recent retrospective case series reported 19 more PV patients who achieved long-term clinical remission with rituximab and IVIG (42% did so after retreatment for relapses).⁴¹

Plasmapheresis has been used as an adjuvant salvage therapy in the treatment of recalcitrant PV by physically removing the circulating pathogenic antibodies.^{42–45} Several small retrospective case series have found clinical improvement in anywhere from 57 to 80% of patients with refractory pemphigus when plasmapheresis has been added to a regimen of steroids and immunosuppressants.^{45–47} Although it lacked the power to address clinical benefit, one randomized controlled trial of 40 patients with PV

evaluated the steroid-sparing benefit of 10 large-volume plasmapheresis procedures when added to prednisolone (n = 19) in comparison with prednisolone alone (n = 15).⁴⁸ The group receiving plasmapheresis did not enjoy a significant steroid-sparing effect and, in addition, had four deaths caused by sepsis, suggesting that the intervention promoted an increased risk of infection.⁴⁸

In general, patients with PV require extensive supportive therapy. Careful attention to wound care is essential in PV given the extensive erosions and ulcerations that occur. The goal is to reduce pain and prevent and treat secondary infections that can delay appropriate response to therapy.⁴⁹ Accordingly, any lesion that does not respond to therapy should be cultured to exclude secondary infection.⁴⁹ Individual lesions recalcitrant to systemic therapy may be treated with topical steroids or intralesional steroid injections.⁴⁹ Randomized, double-blind, placebo-controlled trials have also shown efficacy for epidermal growth factor (10 µg/g)⁵⁰ and nicotinamide 4% gel⁵¹ in the topical treatment of the skin lesions as well as pimecrolimus 1% cream⁵² for oral lesions. Oral lesions may also be treated with high-potency topical steroids in an adherent base, by intralesional steroid injection, or as a dexamethasone 0.5 mg/5 ml oral swish and spit.⁴⁹ Oral care with tooth brushing and the use of antiseptic mouthwashes such as chlorhexidine or hydrogen peroxide solutions should be encouraged to help prevent dental decay.⁴⁹

CONCLUSIONS

On the basis of our review of the cited literature, we agree with the consensus that standard therapy is appropriate for mild to moderate cases of PV. It should be noted that severity classifications are often based on overall clinical impression although several scoring systems exist to provide objective guidance.⁵³ Standard therapy consists of high-dose corticosteroids (1–2 mg/kg/day) with an adjuvant immunosuppressant. While no consensus exists on which immunosuppressant is ideal, the literature suggests starting with mycophenolate mofetil (2 g/day), following it up with azathioprine (2 mg/kg/day), and, finally, cyclophosphamide (2 mg/kg/day), based on their overall side-effect profiles and steroid-sparing effects.¹¹

For cases of severe PV, in patients refractory to standard therapy or in patients who are unstable, the literature favors aggressive use of additional treatments to reduce autoantibody burden and to minimize overall corticosteroid and immunosuppressant use.¹¹ The

literature is replete with case reports of refractory PV responding to rituximab and there is growing interest in the use of IVIG.^{32–41} Though no rituximab-dosing protocol is clearly superior, giving 4 weekly 375 mg/m² doses allows for more rapid redosing and would be more suitable for incorporating IVIG therapy if needed. IVIG is an appropriate option when an increased risk of infection cannot be tolerated because IVIG, theoretically, also confers immunoprophylaxis.⁵⁴ IVIG can be dosed at 2 g/kg delivered over 3 to 5 days and administered in place of the fourth-weekly rituximab dose for the first 2 months.

In the very small set of patients who are pregnant and have severe PV exacerbations, monotherapy with IVIG should be considered. Plasmapheresis may be beneficial as a salvage therapy for refractory cases of pemphigus but requires further evaluation.

It is important to treat severe PV aggressively and to maintain a low threshold to initiate additional therapies such as rituximab and IVIG earlier in the clinical course. If not, the disease process may harden because of epitope spreading, resulting in a loss of disease control and an increase in patient mortality.⁵

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